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ON THE INFECTIVITY OF TABARDILLO OR MEXICAN TYPHUS FOR MONKEYS AND STUDIES ON ITS MODE OF TRANSMISSION.

By JOHN F. ANDERSON, Director Hygienic Laboratory, and JOSEPH GOLDBERGER, Passed Assistant Surgeon, United States Public Health and Marine-Hospital Service.

In two previous notes [a] we reported some results of work upon tabardillo, the typhus fever of Mexico. In the second of these notes we recorded the experimental production of fever after the inoculation with blood from cases of human tabardillo in two species of monkeys, one "Bedalia," a female *Macacus rhesus,* and the other "Jerry," a male *Cebus capuchinus.* In order to determine whether the fever thus produced was tabardillo, we decided to test the immunity of these two monkeys by again inoculating them with virulent blood.

On January 7, 26 days after the subsidence of the fever, "Jerry" was given intraperitoneally 8 cubic centimeters of defibrinated blood from case No. 19. This blood was drawn from the general circulation on the tenth day of the disease, and inoculations with it on ordinary culture media showed no visible growth. The accidental death of the control animal made it desirable to reinoculate this monkey. Accordingly, on January 11, 30 days from the subsidence of the fever, "Jerry" received 7 cubic centimeters of defibrinated blood from case No. 20. This blood was drawn from the general circulation on the eighth day of the disease and inoculations with it on ordinary culture media showed no visible growth.

On the same day 5 cubic centimeters of defibrinated blood from the same case (case No. 20) was injected intraperitoneally into "Bedalia," the female *rhesus,* whose attack of fever subsided critically 23 days before. The temperature of both monkeys was taken twice daily during a period of 14 days following the inoculations. No febrile reaction or other indication of illness was noted during this period, at the end of which we were obliged to terminate our observations. [b]

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[a] Anderson, John F., and Goldberger, Joseph: On the relation of Rocky Mountain spotted fever to the typhus fever of Mexico. A preliminary note. Public Health Reports, vol. 24, Dec. 10, 1909, p. 1861.

Same: A note on the etiology of "tabardillo," the typhus fever of Mexico. Public Health Reports, vol. 24, Dec. 24, 1909, p. 1941.

[b] On account of the illness of one of us (J. G.) it was necessary to terminate the work in Mexico City. Accordingly the experimental animals, with one exception ("Adela"), were shipped to the laboratory in Washington. For a period of five days, therefore, observations on them were necessarily suspended.

PASSAGE.

The succession of events after the inoculation of the two monkeys, "Bedalia" and "Jerry," particularly well defined in the former, with blood that gave no visible growth on ordinary culture media, namely, an incubation period of not less than 5 nor more than 11 days succeeded by a fever of 13 days whose onset, course, duration, and critical defervescence presented a most striking resemblance to the fever curve of this disease in man, as may be seen by comparing charts Nos. 1 and 2, left but little doubt in our minds that the fever produced in these animals although without a discernible eruption was due to the transfer of a living virus.

In order, however, to eliminate any possible doubt, it was decided first to reproduce the fever in two or more animals by the inoculation of virulent blood from a human case and then, if successful, to attempt to transfer the infection from those monkeys to a second series. Accordingly the following experiments were performed:

"Adela," a female *rhesus*, was inoculated intraperitoneally on January 11 with 6 cubic centimeters of defibrinated blood from case No. 20, this being a portion of the same blood as was used for testing the immunity of "Bedalia" and "Jerry." This blood, as has already been stated, was drawn from the general circulation on the eighth day of the disease and on ordinary culture media gave no visible growth. On January 19, 8 days following the inoculation, the temperature of this animal began to rise, reaching a maximum of 40.6° C. on January 25.[a] Simultaneously with the rise in temperature the animal gave other indications of illness, such as diminution of the appetite, thirst, ruffled fur and attitude. On January 23, on the fifth day of illness, about 3 cubic centimeters of urine was obtained and found to contain a small percentage of albumin. The fever ended critically on January 30.

"Maria," a female *rhesus*, was inoculated intraperitoneally on January 11 with 8 cubic centimeters of defibrinated blood from case No. 20, this being another portion of the same blood as was used for the inoculation of "Adela," "Jerry," and "Bedalia." On January 19, eight days after the inoculation, the temperature of the animal began to rise, reaching 40.2° C. on the 24th. The following day the temperature was somewhat lower. After January 25 observation of this animal was suspended and not resumed until the afternoon of January 31, when the temperature was found to be normal and the animal in apparently good health. Beside the elevation of temperature this animal showed symptoms of illness similar to but not so marked as those presented by "Adela." This animal, though inoculated with a larger amount of blood than "Adela," presented the milder reaction. This seems to be worthy of note, inasmuch as Ricketts and Wilder[b] made a somewhat similar observation in their experiments.

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[a] On account of the gravity of her condition, this animal was left in Mexico on our departure for Washington. The temperatures recorded and other observations after January 25 were made and reported to us by Mr. Braulio B. Ramirez, technical assistant in the laboratory of the Superior board of health, to whom we wish here to express our obligations.

[b] Ricketts, H. T.; and Wilder, Russell M.: The typhus fever of Mexico (tabardillo). Journ. Am. Med. Assn., vol. 54, Feb. 5, 1910, p. 463.

In view of the more marked reaction in the monkey "Adela" we selected this animal from which to draw blood for passage to a second series of monkeys. Accordingly, on January 23, four days after the onset of the fever in this monkey, blood was drawn from her heart and at once defibrinated. Eight and one-half cubic centimeters of the defibrinated blood was inoculated intraperitoneally into "Faustinella," a female *rhesus*.

On January 24, five days after the onset of fever, some more blood was aspirated from her heart and immediately defibrinated. Eight cubic centimeters of this defibrinated blood was inoculated intraperitoneally into "José," a male *rhesus*.

In broth and on blood-serum slants neither the defibrinated blood used for the inoculation of "Faustinella" nor that used for the inoculation of "José," gave any visible growth.

These animals were kept under observation up to and including January 25, after which date we were obliged to suspend observations.

Observations were resumed in the afternoon of January 31, at which time (eight days after inoculation) "Faustinella" showed a slight rise in temperature. This animal continued for several days with a somewhat elevated temperature, but gave no other indication of illness.

On resuming observations "José" was found (seven days after inoculation) with a temperature of 40.4° C. In the afternoon of February 2, the temperature reached 40.7° C. Two days later the temperature had dropped 2°. During the height of its fever this animal, with the exception of a slight diminution in appetite, showed but little other indication of sickness.

On February 4 blood was aspirated from the heart, immediately defibrinated, and 6 cubic centimeters injected intraperitoneally into another *rhesus* monkey. This blood was sterile upon ordinary culture media.

It is interesting to note that neither "Faustinella" nor "José" presented marked signs of illness during the period of observation This may possibly be significant, in view of Nicolle's[a] experience indicating an attenuation of the virus by passage through the animals with which he experimented.

We have here then, first, a production of fever in two monkeys induced by a single intraperitoneal inoculation in each of defibrinated blood directly from a human case of tabardillo, after an incubation period of eight days in both animals, the blood used being sterile on ordinary culture media. The onset, course, duration, and defervescence of the fever, as observed in one of these animals ("Adela," chart No. 3) bears a close resemblance to the fever curve for "Bedalia" (chart No. 2) and that frequently observed in human cases (chart No. 1). Second, blood drawn from the heart of one of these monkeys ("Adela") four days after the onset of the fever, and again on the following day, although sterile on ordinary culture media, induced, when inoculated intraperitoneally into the monkeys "Faustinella" and "José," respectively, a fever resembling that of the animal from which the blood originated.

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[a] Nicolle, Charles; Comte, C.; and Conseil, E.: Transmission expérimentale du typhus exanthematique par le pou du corps. C. R. des Acad. Sci., tome 149, No. 10, Sept. 6, 1909, p. 486.

We believe, therefore, that this succession of events justifies the conclusion that in the inoculation of monkey from man, and in the subsequent passage from monkey to monkey, a living virus capable of multiplication was transferred.

FILTRATION.

With a view of obtaining some idea of the size of the infecting agent we performed the following experiment: Six cubic centimeters of blood serum were obtained by centrifugalization of a portion of defibrinated blood from case No. 20, this being a portion of the same blood as was used for testing the immunity of "Bedalia" and "Jerry" and for the inoculation of "Adela" and "Maria." The blood serum was diluted with 12 cubic centimeters of physiological salt solution and then filtered through a Berkefeld filter. Fifteen cubic centimeters of the filtrate, representing approximately 5 cubic centimeters of the serum, was inoculated intraperitoneally into "Esther," a female *rhesus*, on January 11.

The temperature of this animal was taken twice daily up to and including January 25, a period of 14 days, when observations were temporarily suspended. On the afternoon of January 31, when observations were resumed, no febrile reaction or other manifestations of illness were noted. It would appear, therefore, that either the infecting organism is too large to pass through this filter or that it passed through in insufficient numbers to produce a reaction in this animal. Ricketts and Wilder[a] have reported that the virus failed to pass through a Berkefeld filter in an experiment made on the same date (January 11) as the one done by us.

It may be well to note here that portions of the blood serum from case No. 20 on January 11 were used, first, to test the immunity of "Bedalia" and "Jerry;" second, to inoculate "Adela" and "Maria;" and third, for the inoculation of "Esther," after filtration through a Berkefeld filter. As has already been recorded above, the monkeys "Bedalia" and "Jerry" showed their immunity by giving no reaction to the inoculation with this blood; "Adela" and "Maria" both became sick; "Esther," the animal inoculated with the filtered serum, showed no reaction.

INSECT TRANSMISSION.

The peculiarities of the epidemiology of tabardillo must strike even the most casual reader who is familiar with the advances in our knowledge of the rôle of insects in disease transmission as highly suggestive of the existence of an intermediary host. We were very early convinced that this disease is not contagious, using this word in its ordinary sense. We could cite a long series of facts, both from the literature and from our own observations, in support of this view. We shall, however, content ourselves with citing the following:

F. J., adult, American, nonimmune. Lived at a hotel in Mexico City, but came in daily intimate contact with cases of tabardillo between November 22 and December 16, 1909. On the nights of

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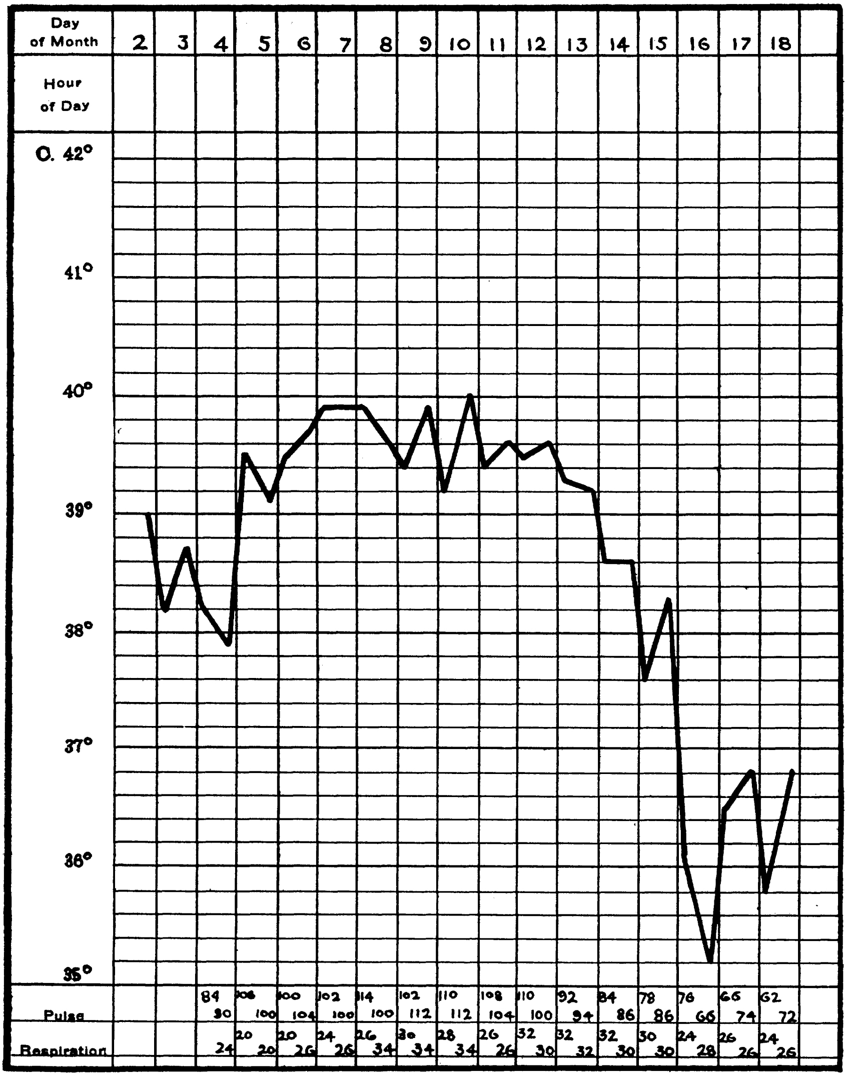
[a] Ricketts, H. T., and Wilder, Russell M.: The typhus fever of Mexico (tabardillo). Journ. Am. Med. Assn., vol. 54, Feb. 5, 1910, p. 463.

CHART NO. 1

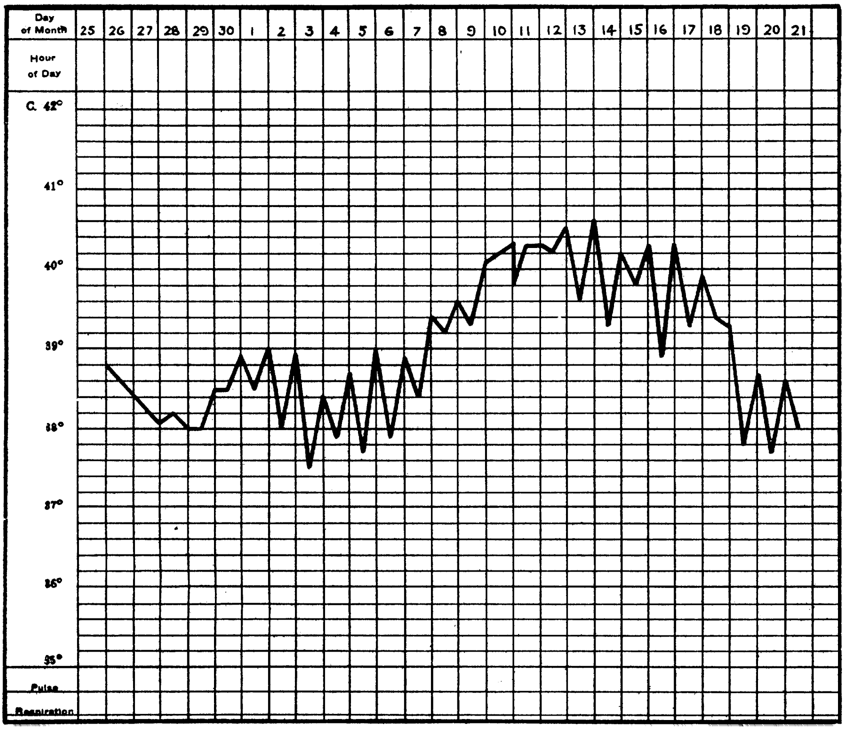
Name..



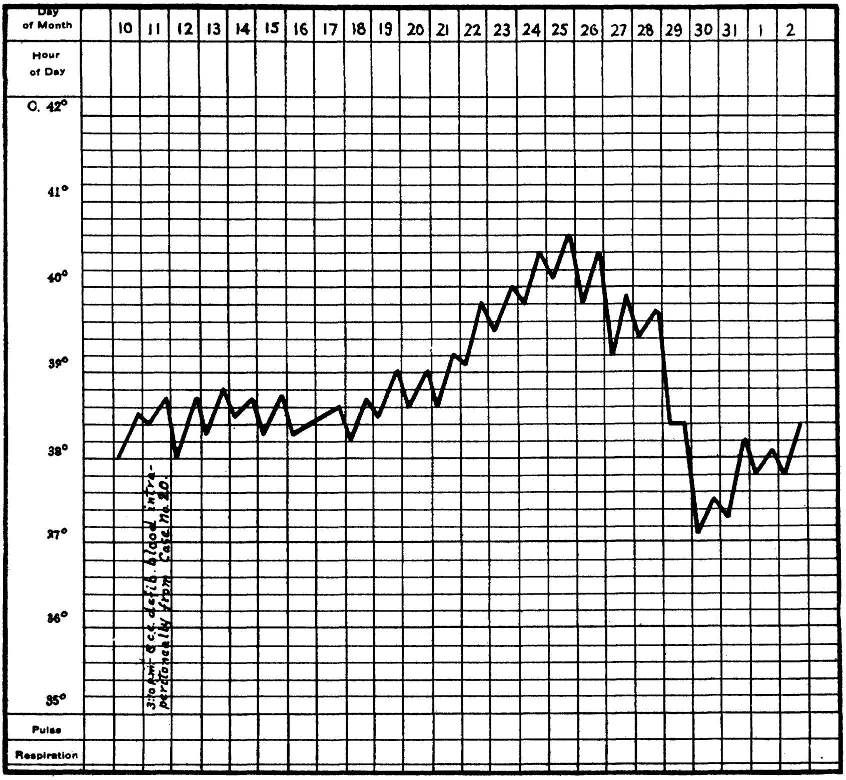
Day of Month	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Pulse			84 80	106 100	100 104	102 100	114 100	102 112	110 112	108 104	110 100	92 94	84 86	78 86	76 66	66 74	62 72	
Respiration			24	20 20	20 26	24 26	26 34	30 34	28 34	26 26	32 30	32 32	32 30	30 30	24 28	26 26	24 26	

Name BEDALIA

CHART NO. 2



Name ADELA CHART NO. 3



January 5 and 6 he slept in a bed that had been occupied on January 2, 3, and 4 by a patient in the first three days of a well-marked attack of tabardillo (chart No. 1). None of the bedding or bedclothes had been in any way disturbed in the interval prior to their use by this individual. At the end of three days the bedclothes were changed, but with this exception the bed and room remained as they had been when occupied by the patient. F. J. inhabited this room for three weeks longer. On careful search no insects other than fleas were found in the room. During a period of observation of 17 days this man continued in his usual health.

The following data, for which we are indebted to Miss Ella Wilson, superintendent of the American Hospital in Mexico City, are significant in this connection. From January 9, 1908, to November 24, 1909, 30 cases of typhus fever had been treated in the typhus pavilion of that hospital. Each of these cases had had a special nurse who was an American nonimmune. None of these nurses contracted the disease.

Having satisfied ourselves that neither contagion in the ordinary sense nor that fomites as usually understood played any rôle[a] in the transmission of the disease, and with the impression strongly in our minds that some intermediary host was the probable transmitting agent of the infection, we took up a consideration of the insects which might be expected to play this rôle. The insects which immediately suggested themselves as worthy of serious attention in this connection were the flea, the bedbug, and the body louse.

The flea.—A review of certain facts enabled us very quickly to eliminate the flea from consideration. The ubiquity of the flea and the well-recognized limitation of the prevalence of the disease in the lowest social classes obviously do not harmonize with the idea that this insect is the transmitting agent. It is a well-recognized fact that in houses and families of the better classes secondary cases are rarely observed, though far from being free from infestation by fleas. Furthermore, it is a well-recognized fact that the striking distance of the infection is decidedly circumscribed, a fact with which the agility of the flea also does not harmonize.

The bedbug.—This insect is only a temporary parasite of man. As is well known, it lurks and hides in cracks and crevices and in the folds of bedding during the day, coming out at night to feed, retiring again toward morning. It is only rarely that it remains on the body of an individual. With this in mind, and assuming for the moment that the bedbug is the carrier, tabardillo should have the characteristics of a house disease, i. e., the infection should appear to be attached to houses and practically not at all to individuals, such as is the case in yellow fever. As a matter of fact, however, such is not the case. The distribution of the bedbug among the social classes is much more general than tabardillo, which, in a general way, is fairly limited to the poverty-stricken portion of the population. These facts appear to us to rule out this insect as the probable transmitter of tabardillo.

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[a] As a matter of fact, we believe that both contact with individuals and fomites play a rôle in this disease, but only in the sense that by contact with individuals and fomites (lice-infested clothes or bedding) the transfer of the louse to another individual is favored.

Finally, both the bedbug and the flea seem to us to be pretty definitely ruled out of consideration by the further fact that these insects are found in the lowlands of Mexico, where the disease is unknown except as isolated imported cases.

The body louse.—Having eliminated the flea and the bedbug as the probable transmitters of the disease, there remains for consideration only the body louse (*Pediculus vestimenti*). This insect, as is well known, is parasitic on man, but may be said never to occur on persons or classes of people of cleanly habits. This fact may be seen very clearly in Mexico and is in entire harmony with the distribution of the disease among the social classes.

Students of the epidemiology of typhus fever have long observed that the disease, while apparently highly contagious, requires a fairly intimate contact for this contagiousness to manifest itself. Now, the body louse is a relatively sluggish insect. It practically makes only short excursions in the seams of the clothing of the individual and from these to the body of its host to feed. Its transfer from person to person takes place only when individuals are in close association with one another or with infested clothes, or when the insect is accidentally dislodged from the body of its host and is subsequently picked up, as it were, by another person.

Impressed by these considerations we attempted to transmit the disease by means of the body louse, *Pediculus vestimenti*, from man to monkey. For this purpose we obtained a considerable number of these insects and distributed them in small wide-mouthed bottles, carefully stoppered. Two of these bottles were kept, during the day, at a temperature of 24° to 27° C., and at night at approximately 18° to 20° C. These lice were allowed to feed repeatedly upon the monkey "Jane," to which reference will shortly be made. After 21 days three survivors were killed and preserved. Two other bottles, containing some of the same original collection of lice, were kept day and night close to the body of one of us, with the idea that this was a more suitable temperature for them. At the end of 36 hours, although having received a feeding during this interval, all the insects were found dead.

At this stage of our work, Nicolle's [a] papers first came to our attention. In one of these he reported the successful transmission of typhus fever, in Tunis, from monkey to monkey, the *Macacus sinicus*, by means of the body louse, and we noted that his lice between feedings were kept at a temperature of 16° to 20° C. This suggested to us that probably the cause of the death of the lice in the two bottles which we had kept continuously at approximately body temperature was due to too high a temperature. We decided, therefore, to repeat the experiences of keeping the lice at approximately body temperature by placing another batch of these insects in two flasks and keeping them close to the body day and night. The result of this experiment was practically identical with our first experience. Only a few of the insects survived 48 hours, although, as in our first experience, they had been fed in the interval.

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[a] Nicolle, Ch.: Reproduction experimentale du typhus exanthematique chex le singe; Compt. Rend. Acad. des Sciences, vol. 149, July 12, 1909, p. 157.

Nicolle, Ch., Comte, C., and Conseil, E.: Transmission experimentale du typhus exanthematique par le pou du corps; Compt. Rend. Acad. des Sciences, vol. 149, Sept. 6, 1909, p. 486.

Several batches of the same collection of lice as were used for this experiment were kept at a temperature of 14° to 20° C. They were allowed to feed daily, and among these the mortality was comparatively slight. This influence of temperature on the longevity of the louse seems to us strikingly significant in relation to the apparently singular limitation of the disease to the Mexican plateau, i. e., to places having an altitude of not less than 1,500 to 1,800 meters, and its complete absence from lower altitudes, and in relation to its seasonal prevalence.

The peculiar limitation of the disease to places at a considerable altitude, as just stated, had been engaging our attention, and with the idea of the possibility that the body lice in places in the lower altitudes were perhaps of a different species from those on the plateau, we endeavored to obtain specimens in Tampico through the courtesy of the Rev. Neill E. Pressly, whose duties bring him into close and confidential relations with the natives. Replying to our communication, Mr. Pressly informed us that the body louse was practically unknown in that locality. Subsequently this was confirmed by Doctor Rolph, a physician located on a large ranch near Tampico. This gentleman, in conversation with us, stated that body lice did not exist in his locality, though head lice were common. He added, further, that this was so well known among the natives that when peons from the plateau in search of work arrived infested with body lice, they declined to take any special measures for the destruction of these parasites on the ground that the lice could not live there more than a few days, and such he actually found to be the case.

As already stated, we attempted to transmit the disease from man to monkey by means of the louse *Pediculus vestimenti.* The lice used for this purpose were obtained from the clothing of persons of a class in whom the infection is common. It was, therefore, quite possible, and indeed probable, that some of these may have already been infected. Before applying them to the monkey in the course of the experiment, we permitted them to feed on cases of tabardillo.

Experiment No. 1: "Jane," a female *Macacus cynomolgus,* was repeatedly exposed to the bites of several batches of lice obtained as above described. These lice, before being applied to the monkey and at various intervals in the course of the experiment between November 28 and December 31, had bitten cases of tabardillo in the first stages of the disease. The lice were applied to this animal in all thirty times. During the first 16 days of the experiment a single batch of lice (the first) was used throughout, and was kept at a temperature during the day of 24° to 27° C. and at night at 18° to 20° C. The several batches of lice later used were kept at a temperature of 14° to 22° C. The animal was kept under observation for 25 days after being last bitten by the lice. Then, after an interval of 5 days, during which time the observation was suspended, for a further period of 12 days. Throughout the period of observation this animal showed no abnormal elevation of temperature or other indications of illness. This experiment appears to have resulted negatively.

We regret that we have been unable to test the susceptibility of this monkey to blood inoculation; but inasmuch as it is specifically more closely related to the *Macacus rhesus* than the capuchin monkey, both of which species we have shown to be susceptible to blood inoculation, it seems, *a priori*, reasonable to assume the existence of such susceptibility in this species.

Experiment No. 2: "Raquel," a female *rhesus*, was exposed on 6 successive days to the bites of lice which had been twice allowed to feed upon case No. 19, and the third time upon case No. 20. Eight days after the last exposure the evening temperature of this animal rose to 39.6° C.; the following day it was 39.1° in the morning and 39.6° in the evening. These temperatures were a little above the normal range for this animal, but on the tenth day after the last exposure (January 25) the temperature of the animal had dropped back to within the limits of its normal range.

After this we were obliged to suspend observations for 5 days, when they were again resumed. The temperature of the animal was normal, and it presented no indications of illness. Whether the slight rise in temperature here recorded was the beginning of a brief reaction or not we are unable to say.

THE RELATION OF TABARDILLO TO EUROPEAN TYPHUS.

Several distinguished Mexican clinicians have raised the question as to the identity of tabardillo and European typhus, basing their doubts as to the identity on certain apparent clinical differences in the two diseases. Certain differences in the results of our work and that of Nicolle would seem to give some experimental support to this view. Nicolle has reported that he was unable to inoculate monkeys of the species *Macacus sinicus* by blood directly from the human subject, but was obliged first to pass it through a chimpanzee, whereas we have been able to infect not only a closely related species, the *Macacus rhesus*, but also a *Cebus capuchinus*, directly with blood from a human case of tabardillo.

It is interesting to note, however, that the mode of transmission of European typhus and tabardillo is probably the same. Nicolle has reported a successful experiment with the body louse, and both Ricketts and Wilder and ourselves have independently come to regard this insect with grave suspicion as playing the same rôle in the Mexican disease.

SUMMARY AND CONCLUSIONS.

1. At least two species of monkeys, *Macacus rhesus* and *Cebus capuchinus*, are susceptible to direct inoculation with the blood from human cases of tabardillo.
2. One attack of the disease in the monkey produced by blood inoculation directly from man induces a definite immunity to a subsequent inoculation with virulent blood. The reaction following blood inoculation in monkeys "Bedalia" and "Jerry," reported in our second note, was therefore the first recorded experimental production of tabardillo in monkeys.
3. The blood from human cases of tabardillo is infective on at least the eighth day of the disease. It seems probable, however, that it will be found infective throughout the active febrile stage of the disease.
4. The blood from the monkey, *Macacus rhesus*, is infective by passage to a second monkey of the same species on at least the fifth and sixth days of the disease.

5. Diluted blood serum from a human case of tabardillo, when passed through a Berkefeld filter, failed, when inoculated into a monkey, to produce the disease.

6. The blood of a monkey of the species *Macacus rhesus* is infective, though its infectivity is somewhat attenuated, to a second monkey of the same species.

7. The disease is not conveyed by fomites, as such, nor is it contagious in the ordinary sense of the word.

8. The epidemiological facts of the disease, in our opinion, point unmistakably to an insect intermediary; and we believe that our observations point strongly to the body louse (*Pediculus vestimenti*) as this insect.

9. We are of the opinion that the evidence against the body louse as transmitter of tabardillo is sufficient to demand that prophylactic sanitary measures directed against this disease should take into consideration that insect.